Journal of Vessels and Circulation
Qom University of Medical Sciences
Summer 2023. Volume 4. Number 3

Research Paper

Therapeutic Potential of Plasma Exchange, Systemic Corticosteroids, and, Interferon for Severe COVID-19: A Non-randomized Controlled Trial

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Please cite this article as Adeli SH, Parham M, Asghari A, Tabaraii R, Shajar R, Abadpoor Z, et al. Therapeutic Potential of Plasma Exchange, Systemic Corticosteroids, and, Interferon for Severe COVID-19: A Non-randomized Controlled Trial. J Vessel Circ. 2023; 4(3):123-132. http://dx.doi.org/10.32598/JVC.4.3.154.1

http://dx.doi.org/10.32598/JVC.4.3.154.1

Article info:
Received: 21 Jan 2023
Accepted: 04 Mar 2023
Publish: 01 Jul 2023

Keywords:
COVID-19, Plasma exchange, Corticosteroids, Interferon, Hospitalization, Mortality rate

ABSTRACT

Background and Aim: Since 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has spread systematically, causing extensive immune responses and significant damage to other organs. This non-randomized, open-labeled, clinical trial was conducted to evaluate the effect of therapeutic plasma exchange (TPE) on critically ill coronavirus disease 2019 (COVID-19) patients.

Materials and Methods: This single-center clinical trial was performed at Shahid Beheshti Hospital affiliated with the Qom University of Medical Sciences, from March to June 2020. A total of 60 patients with serious or life-threatening COVID-19 infection were included in the study. Patients in the intervention group (30 patients) received systemic corticosteroids and interferon and TPE were performed for them.

Results: Of the 60 patients studied, 48% died, while about 52% were discharged. Mortality was significantly lower in the intervention group than in the control group (20% vs 77%, respectively). The severity of the disease was significantly lower in the intervention group than in the control group (20% vs 77%, respectively), although the median days of hospitalization and ICU admission were higher in the intervention group than in the control group. No side effects were observed in the intervention group during the first 72 hours after TPE.

Conclusion: TPE can provide a longer lifeline and a lower mortality rate in critically ill COVID-19 patients. Therefore, we recommend that TPE, systemic corticosteroids, and interferon, along with other standard treatments, be used as part of the treatment protocol for critically ill COVID-19 patients.

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Introduction

In 2019, a series of pneumonia cases with unknown etiology were reported in Wuhan. The disease was later named COVID-19 by the World Health Organization (WHO) [1-3]. The virus causing coronavirus disease 2019 (COVID-19) spread and caused a global pandemic [4-6].

Coronaviruses are enveloped, positive-sense, single-stranded RNA viruses with size variations [2, 7]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a member of the family of viruses known as coronaviruses that infect humans and, like SARS-CoV and MERS-CoV, affects the lower respiratory tract [4].

The clinical manifestations of COVID-19 ranged from mild to severe. Symptoms usually appear 2-14 days after exposure to the virus and include fever, cough, dyspnea, and myalgia. It is currently estimated that about 81% of people with severe COVID-19 experience complications, including acute respiratory distress syndrome (ARDS), shock, acute hepatic injury, and secondary infection that can lead to death [5, 8].

Some studies have demonstrated that the viremic phase was not the cause of death in critically ill patients. Many critically ill patients did not exhibit severe symptoms in the early stages of the disease; instead, their condition suddenly worsened in the later stages of the disease or during the recovery process. ARDS and multiple organ failure can occur rapidly, resulting in death within a short time [9]. The mortality rate of COVID-19 has reportedly ranged from 0 to 14.6% [1]. However, Yang et al. reported that among adult ICU patients with COVID-19, 32 of 52 patients (61.5%) died within 28 days [10]. In another studies, the mortality rate of hospitalized patients (28%) was much higher than in other reports where the follow-up data were incomplete [11-13].

One of the causes of the high mortality associated with this disease is its complex pathogenesis. The pathogenesis of COVID-19 and its severe episodes result from the direct cytolytic effects of SARS-CoV-2 and the adverse consequences of the immune response. At first, the virus binds to pneumocytes and ciliated bronchial cells via human angiotensin-converting enzyme 2 (ACE2) and infects them [14, 15]. The second phase, "immune system dysfunction", involves a virus-induced cytokine storm and an imbalance in reactive oxygen species (ROS) production, resulting in inflammation and tissue destruction. Additionally, excess ROS synthesis contributes to the suppression of the immune system due to the paralysis or destruction of cytotoxic CD8 T cells and CD4 helper T cells. Pathological coagulation has also been shown to play an important role in the pathogenesis of this disease, with a hypercoagulable state observed in many critically ill patients. The underlying mechanisms are unclear but likely include virus-induced inflammation of blood vessels and immunothrombosis caused by immune stimulation.

SARS-CoV-2 is not confined to lung tissue but spreads systematically, causing extensive immune responses and significant damage to other organs, including the brain, heart, blood vessels, liver, and kidneys [14]. The levels of plasma cytokines and chemokines, including interleukin-2 (IL2), IL7, IL10, granulocyte-colony stimulating factor (GSCF), IFN-γ-inducible protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α), and TNFα are higher in ICU patients [16].

Cytokine storm plays a key role in the severe pathogenesis of COVID-19 and is one of the most important causes of ARDS and multiple organ failure. It plays an important role in disease exacerbation [17].

Effective treatment for COVID-19 should include a strategy to suppress the inflammatory response, halt virus replication, and remove pre-formed cytokines. Also, suppressing cytokine storms can play an important role in the treatment of COVID-19 patients and can save their lives [17, 18]. Immunosuppressive agents, such as methylprednisolone and tocilizumab have shown beneficial effects against COVID-19 [19, 20]. Plasma exchange offers multiple benefits by uniquely eliminating inflammatory cytokines and ROS while also addressing the hypercoagulable state uniquely [18].

During this pandemic, we had successful experiences treating critically ill patients with plasmapheresis, corticosteroids, and interferon, and we published the initial results in a case series [21]. The present study is a continuation of our previous studies, which aimed to investigate the effect of this method on critically COVID-19 patients.

Materials and Methods

Study design and setting

The present single-center, non-randomized, controlled, open-label clinical trial was conducted at Shahid Beheshti Hospital affiliated with Qom University of Medical Sciences, Qom, Iran, from March to June 2020. In

this study, the inclusion criteria were as follows: Patients aged ≥18, patients with serious COVID-19 infection (mild to severe ARDS based on PaO_2/FiO_2), and definitive SARS-CoV-2 infection confirmed by real-time polymerase chain reaction (RT-PCR) assays.

Additionally, patients with shock, central line intolerance, a previous allergic reaction to plasma exchange or its components, sodium citrate, plasma products, or a history of allergy to FFP or alternative fluids, such as colloids and albumin, as well as a history of allergy to heparin, hypocalcemia, and known immune suppression/deficiency status, were included at the discretion of the attending physician. Exclusion criteria included patients who refused to participate in the study.

Patients' informed consent was obtained before the study. Demographic information of patients, such as age, sex, the presence of underlying diseases and their types (diabetes, hypertension, ischemic heart disease, and obstructive airway disease), as well as oxygen saturation percentage and quick sequential organ failure assessment score (qSOFA score) were recorded at baseline for all patients. The qSOFA score [22] is a simplified version of the SOFA Score that is used as a primary method to identify high-risk patients for poor outcomes due to infection. The qSOFA score consists of three clinical criteria, each of which has a score. These criteria include low blood pressure (systolic blood pressure (SBP) ≤100 mm Hg), high respiratory rate (≥22 breaths/min), and altered mentation (Glasgow Coma Scale (GCS) ≤14). Patients with two or more of these criteria are at high risk for poor outcomes.

The primary outcomes of this study included the mortality rate (both in the hospital and up to three months after discharge), disease severity after receiving the intervention (based on the qSOFA score), duration of admission in the intensive care unit, and length of hospitalization. The secondary outcomes included laboratory parameters, such as WBC count, lymphocyte count, platelet count, hemoglobin level, creatinine, and international normalized ratio (INR), which were measured at baseline and on the day of discharge.

To assess the safety of TPE, side effects of apheresis and plasma replacement were recorded for up to 72 hours. Side effects, such as shock during apheresis, electrolyte imbalance, and worsening of respiratory status were monitored for 72 hours after TPE. Patient follow-up was performed based on symptom remission, improved respiratory status, and CT scan findings.

Sample size

This study is a non-randomized controlled two-arm trial. A total of 60 patients with serious or life-threatening COVID-19 infections were included in the study. Thirty patients were in the intervention group, while another thirty patients were in the control group. The sample size was not determined based on statistical power calculations. Critically ill patients who had moderate to severe ARDS (based on PaO_2/FiO_2) after receiving the standard protocol of interferon and corticosteroids for three days, and who still required respiratory support and intubation, were eligible for TPE and assigned to the TPE group.

Interventions

All patients enrolled in this study received routine COVID-19 treatments according to institutional, national, and international recommendations, along with standard supportive care. The treatment plan for these patients consisted of a single dose of 400 mg hydroxychloroquine sulfate, 500 mg naproxen BID, and 100/400 mg lopinavir/ritonavir BID for five days. Patients in the intervention group received systemic corticosteroids (4 mg dexamethasone TDS) and interferon (three doses of 250 µg interferon-βevery other day) in addition to standard treatment, and TPE was performed for them.

The TPE protocol involved plasmapheresis, with two liters of filtration daily, compensated with 4-5 units of fresh frozen plasma (FFP), 5 vials of albumin, and one or two 10-20 cc doses of calcium gluconate (20%), depending on the patient's serum calcium level. The remaining volume was replaced with normal saline, according to the patient's volume status. Each plasmapheresis session lasted four hours. For the intervention group, four to five plasmapheresis sessions were performed daily. TPE was conducted using an Apheresis device (Haemonetics MCS plus; United States). Conditions for discontinuing plasmapheresis included any sudden change in the patient's condition or the appearance of red flags (e.g. dyspnea, seizures, chest pain, and hypotension unresponsive to one or two fluid boluses). During plasmapheresis, patients' vital signs were monitored every 10 to 15 minutes.

Statistical analysis

For descriptive reporting of the data, frequency, percentage, Mean±SD were used. The differences in frequency of the variables between the studied groups were evaluated using the chi-square test. The mean difference was evaluated using a t-test when the quantitative variable had a normal distribution and a Mann-Whitney U

Table 1. Demographic characteristics of COVID-19 patients

Variables	Mean±SD/No. (%)			P
	Total (n=60)	Plasmapheresis (n=30)	Control (n=30)	
Age (y)	51.45±16·61	48.03±16·44	54.87±16·34	0.112
Gender	35(58.33)	18(60)	17(56·67)	0.793
Underlying disease	31(51.67)	15(50)	16(53·33)	0.796
Diabetes	18(30)	8(26·67)	10(33·33)	0.573
Hypertension	17(28.33)	9(30)	8(26·67)	0.774
Ischemic heart disease	12(20)	8(26·67)	4(13·33)	0.197
Obstructive airway disease	4(6.67)	2(6.67)	2(6.67)	1.000
SPO_2, median (IQR)	81.50 (78.25-87)	80 (77.50-84.25)	84 (80-88)	0.068
qSOFA score on admission	36(60)	27(90)	9(30)	<0.001
ICU admission	40(66·67)	19(63·33)	21(70)	0.584

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Abbreviations: qSOFA: Quick sequential organ failure assessment; IQR: Interquartile range; ICU: Intensive care units.

test when the normal distribution condition was not met. The normal distribution of variables was assessed using the Shapiro-Wilk test. In all analyses, a significance level of P<0.05 was considered. Analyses were performed using SPSS software, version 26.

Results

A total of 60 patients with COVID-19 were included in this study. The mean age of these patients was 51.45±16.61 years, and their median blood oxygen saturation level ranged from 58% to 81.5%. Also, 35 patients were male, and 51.67% (31 cases) had underlying diseases, while 60% (36 cases) had high-risk infections based on the qSOFA score. About 67% (40 cases) of patients had a history of hospitalization in the intensive care unit (ICU) (Table 1).

There was no significant difference in outcome-affecting variables (Such as age, sex, underlying diseases,

Table 2. Clinical outcomes of COVID-19 patients

Variables		No. (%)/Median (IQR)			P
		Total (n=60)	Plasmapheresis (n=30)	Control (n=30)	
Outcome	Expired	29(48.33)	6(20)	23(76.67)	<0.001
	Discharged	31(51.67)	24(80)	7(23.33)	
qSOFA score[n]	Low-risk	31(51.67)	24(80)	7(23.33)	<0.001
	High-risk	29(48.33)	6(20)	23(76.67)	
	Day of hospitalization	10 (5-16.75)	14 (10.75-20.25)	5 (4-9.25)	<0.001
	Day of ICU admission	6 (3-12.5)	7 (6-21)	3 (2-5)	<0.001

[n]At the time of discharge or expired day.

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Abbreviations: qSOFA: Quick sequential organ failure assessment; IQR: Interquartile range; ICU: Intensive care units.

Table 3. Laboratory findings of COVID-19 patients

Variables	Before Treatment				After Treatment			
	Median/Mean±SD			P	Median/Mean±SD			P
	Total (n=60)	Plasmapheresis (n=30)	Control (n=30)		Total (n=60)	Plasmapheresis (n=30)	Control (n=30)	
WBC (×10^9/L) (IQR)	9050 (6825-12975)	8950 (6650-11850)	10700 (6475-14125)	0.308	11300 (8525-15075)	12000 (9800-15000)	10200 (7950-15575)	0.348
Lymphocyte (×10^9/L) (IQR)	800 (500-1000)	800 (500-900)	865 (537.50-1200)	0.146	1150 (800-1300)	1200 (1100-1200)	900 (600-1525)	0.137
Hemoglobin (g/dL)	12.44±2.40	12.32±2.03	12.55±2.75	0.718	11.65±1.99	12.01±1.77	11.28±2.16	0.156
Platelet (×10^9/L) (IQR)	203500 (162-289500)	208500 (172500-284000)	203500 (150500-298750)	0.756	220613.33 (116285.98)	217400 (105374.41)	223826.67 (128007.88)	0.833
Creatinine (mg/dL) (IQR)	1.10 (1-1.30)	1.10 (0.90-1.20)	1.15 (1-1.55)	0.199	1.10 (0.90-1.77)	0.95 (0.80-1.27)	1.40 (1-2.52)	0.013
INR (IQR)	1.10 (1-1.23)	1.20 (1.10-1.30)	1.10 (1-1.21)	0.073	1.20 (1.10-1.30)	1.20 (1.10-1.20)	1.21 (1.10-1.36)	0.042

Abbreviations: WBC: White blood cells; INR: International normalized ratio; IQR: Interquartile range.

blood oxygen saturation level, and history of hospitalization in the ICU) between the intervention and control groups (P>0.05). However, the severity of the disease was significantly different between the two groups (P<0.001). The number of critically ill patients in the intervention group was significantly higher than that in the control group (90% vs 30%, respectively) (Table 1).

Overall, among the 60 patients studied, 48% (29 cases) died and about 52% (31 cases) were discharged from the hospital. Mortality was significantly different between the two groups (P<0.001). This proportion was significantly lower in the intervention group than in the control group (20% vs 77%, respectively). Also, the severity of the disease after treatment was significantly different between the intervention and control groups (P<0.001), with the severity being significantly lower in the inter-

Table 4. Analysis of ICU parameters of COVID-19 patients

Outcomes	ICU Admission			P	Non-ICU Admission			P
	No. (%)/Median				No. (%)/Median			
	Total (n=40)	Plasmapheresis (n=19)	Control (n=21)		Total (n=20)	Plasmapheresis (n=11)	Control (n=9)	
Expired,	26(65)	6(31.58)	20(95.24)	<0.001	3(15)	0(0)	3(33.33)	0.038
Discharged	14(35)	13(68.42)	1(4.76)		17(85)	11(100)	6(66.67)	
Day of hospitalization (IQR)	9.50 (5-18.75)	14 (10-24)	5 (4-9)	<0.001	11.25 (6.70)	15 (6.15)	6.67 (4.06)	0.003
Day of ventilator use (IQR)	4.50 (3-7)	7 (4-16)	3 (2-5)	0.001	0 (0-0)	0 (0-0)	0 (0-0.50)	0.109

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vention group than in the control group (20% and 77%, respectively). A significant difference was also observed in the number of hospitalization and ICU admission days among the two groups (P<0001). The median days of hospitalization and ICU admission were higher in the intervention group than in the control group, respectively (14 days vs 5 days) and (7 days vs 3 days) (Table 2).

Laboratory findings did not significantly differ between intervention and control groups. Although the amount of blood cells was lower in the intervention group at baseline, this difference was not statistically significant (Table 3). After treatment, the number of blood cells in the intervention group was higher than in the control group; however, this difference was not significant (Table 3).

Analysis of ICU parameters showed that mortality among ICU patients in the intervention group was significantly lower than in the control group (P<0.001). In the intervention group, 31% of patients admitted to the ICU died, while this proportion was 95% for the control group. This difference in mortality was also observed in patients who were not admitted to the ICU (P=0.038). Mortality in the non-ICU hospitalized intervention group was 0%, compared to 33% in the control group (Table 4).

No side effects were observed in the intervention group during the first 72 hours after TPE. Also, in the three-month follow-up, the mortality rate after discharge in the control group was 28.57% (two cases out of seven patients), while in the intervention group, it was 4.17% (one case out of 24 patients).

Discussion

COVID-19 has become one of the leading causes of mortality in the world in recent months. Numerous studies are underway globally to find solutions that will reduce the mortality associated with the disease. This study non-randomized, open-labeled, prospective clinical trial was conducted to evaluate the effectiveness of TPE in critically ill patients.

In our study, TPE, systemic corticosteroids, and, interferon decreased the mortality rate in the ICU-admitted patient in the intervention group by up to 31.58%. For patients in the control group, this value was 95.2%, meaning that out of 21 patients in the control group who were admitted to the ICU, only one patient survived. This intervention also served as a rescue treatment for non-ICU patients; 11 patients in the intervention group who were not admitted to the ICU survived. However, the mortality rate for patients in the control group who were not admitted to the ICU was 33.3%. After this intervention, the severity of the disease in the intervention group was significantly lower than in the control group, even though the patients in the intervention group were more severely ill before the intervention. Patients who underwent TPE had a longer hospital stay; because the number of deaths in the first days of hospitalization was higher in the control group. Thus, this treatment, as a survival enhancer, increased the length of hospitalization time.

The severity of the disease was significantly different between the intervention and control groups. This difference is because of the study's non-randomization, which was necessitated by medical ethics. TPE is an intensive treatment, and we were only permitted to administer it to patients who met its indications. An unexpected and interesting finding was that, although the patients in the intervention group had significantly more severe disease, they exhibited a lower mortality rate (P<0.0001).

The results of the study were satisfactory. Patients well responded to the treatment, and this intervention reduced mortality in critically ill patients as a rescue treatment. This dramatic response to TPE, systemic corticosteroids, and, interferon is likely due to the intervention's ability to negate several mechanisms of COVID-19 pathogenesis. COVID-19 caused damage or organ failure through different mechanisms, one of the most important being the cytokine storm [23]. TPE reduces inflammation and improves the patient's condition by removing cytokines and inflammatory mediators. In addition to its ability to remove cytokines and chemokine, TPE can remove viral RNAs. Viral RNAs induce hypercytokinemia and hyperketonemia. Therefore, by removing viral RNA and proinflammatory molecules, the production of inflammatory molecules will likely cease.

It should be noted that our patients also used corticosteroids to prevent the production of inflammatory molecules. Therefore, TPE reduces the inflammatory load by removing the inflammatory molecules and prevents their future reproduction by eliminating pro-inflammatory mediators [24]. Immunoglobulins are also removed by TPE. Studies have shown that high serum levels of M and G immunoglobulin are associated with increased mortality in COVID-19 patients [25-27]. Seventy-five percent of IgM is present in the intravascular space, making plasmapheresis more effective at removing IgM. This percentage is 45% for IgG [28]. This is likely an advantage for TPE, as it removes a significant amount of immunoglobulins, thereby affecting the prognosis of the

disease, while still leaving an acceptable percentage of IgG to maintain the patient's long-term immunity. One of the causes of multiorgan failure in COVID-19 is endothelial activation and a hypercoagulation status [29].

Autopsy studies in COVID-19 have shown that one of the causes of lung failure in these patients may be the formation of microthrombi in the pulmonary artery [30]. TPE modulates the coagulation status by removing the molecules involved in the coagulation process and replacing them with FFP. In addition, large molecules that cannot be removed by hemodialysis, such as vWF, are removed by TPE. High levels of vWF cause a hypercoagulation state, as well as endothelial and macrophage activation [31]. In a case series, it was claimed that plasmapheresis and low-dose corticosteroids increase the survival of people with secondary hemophagocytic lymph histiocytosis (sHLH) due to COVID-19 by removing vWF [32]. The production of free radicals is another mechanism of COVID-19 pathogenesis, and TPE neutralizes this pathogenesis by reducing and blocking free radical damage [33]. Although viremia and direct cell damage are less significant in the pathogenesis of severe forms of the disease, part of the effectiveness of TPE may be due to reduced viral load. Ishikawa et al. showed that plasmapheresis can remove hepatitis C virus particles from the blood [34]. Given that the hepatitis C virus has a diameter of 55 to 60 nm, the COVID-19 virus, which ranges from 60 to 120 nm, is likely large enough to be removed by plasmapheresis. In addition to TPE, interferon administration also plays an important role in reducing viral load in these patients.

The effectiveness of TPE for other viruses has been reported in various studies. TPE has a positive effect on the treatment of patients with SARS and MERS [35, 36], belonging to the coronavirus family. Also, during the H1N9 flu outbreak, several studies were conducted on the effectiveness of TPE, all of which yielded satisfactory results [37]. Recently, a limited number of case studies have reported the effect of TPE on the treatment of patients with COVID-19 [38, 39].

Conclusion

This study is the first clinical trial of this sample size to evaluate the effects of TPE on critically ill patients with COVID-19. The results of the study are remarkable and important because they may negate several mechanisms of COVID-19 pathogenesis and, as a lifeline, reduce the mortality of critically ill patients. Therefore, we recommend that TPE, systemic corticosteroids, and interferon, along with other standard treatments, become part of the treatment protocol for critically ill patients.

Ethical Considerations

Compliance with ethical guidelines

The study process and possible complications were explained to patients and they were asked to sign the written consent forms if they were willing to participate in the study. The study protocol was designed based on the Helsinki Declaration for ethical considerations and approved by the Ethics Committee of Qom University of Medical Sciences, Qom, Iran (Code: IR.MUQ.REC.1399.057). The study was also registered at the Iranian Registry of Clinical Trials (IRCT) (Code: IRCT20160118026097N5). This study adhered to CONSORT guidelines.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

The authors are grateful to the Clinical Research Development Unit at Shahid Beheshti Hospital affiliated with the Qom University of Medical Sciences, Qom, Iran, for their support.

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